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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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07/984,264 12/01/92 EKINS

R	5142
EXAMINER	
WOODWARD, M	

18N1/0823

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ART UNIT	PAPER NUMBER
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1813
DATE MAILED:

12

08/23/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 12/1/92
12/31/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-28 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-11 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 12-28 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Applicant's arguments filed December 1, 1992 and December 31, 1992 have been fully considered but they are not deemed to be persuasive.

The objection to the specification under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure is withdrawn. Applicant has not made any factual misstatements in regard to the prior art cited in the Background of the Invention.

The previous rejection made under 35 USC §103 is modified to directly rely on Chang (US Patent 4,591,570).

The following is a quotation of the first paragraph of 35 U.S.C. § 112: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

On page 5 of the specification applicant calculates the value of 0.1 V/K and 0.01 V/K when the sample volume is 1 mL and for affinity constants of 10^{11} , 10^{13} , and 10^8 . The examiner does not obtain the same values when employing applicants formula, e.g. for K equal to 10^8 the examiner obtains values of approximately 6×10^{11} and 6×10^{10} respectively. Since applicant views the limitation to 0.1 V/K as critical to the invention it is essential to

clarify this point and establish where in the specification there is a teaching to permit the proper calculation of 0.1 V/K.

Applicant does not set forth the conditions under which a value of greater than 10^4 molecules is needed in order for the assay to function.

5 Claims 12-28 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

10 A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in
15 the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

20 Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

25 Claims 12-28 are rejected under 35 U.S.C. § 103 as being unpatentable over the combined teachings of Ekins (WO 84/01031) and Chang (US Patent 4,591,570).

The instant claims are to methods, devices for practicing said methods and kits therefor wherein the amount of capture reagent for an analyte is such that an insignificant portion of the analyte present is removed from solution. In

such situations the method becomes volume independent above a minimum volume. Essentially the error due to volume variation is insignificant. At what point error becomes insignificant is operationally defined; although it would appear to be true that the smaller the error the less significant.

5 In WO 84/01031 Ekins teaches, starting from the Law of Mass Action, that if the amount of antibody is sufficiently small that measurements of the amount of analyte bound thereto will be independent of volume (summarized in the abstract). Applicant has admitted these teachings as prior art. In the example of WO 84/01031 less than 10 fmoles of immobilized antibody with an
10 affinity of 2×10^{10} L/M was employed with sample volumes of 0.2, 0.4 and 0.8 mL and it was stated that the measured concentration was the same for each volume within experimental error. The value of V/K for 0.2mL is 10 fmole. Ekins does not disclose over what area the antibody is immobilized nor how the amount of antibody immobilized was determined. Ekins suggests detecting
15 bound analyte using fluorescently labelled reagents (page 5 of WO 84/01031) and a surface containing a plurality of sites.

 Chang teaches a device with a plurality of immobilized antibodies wherein the site of immobilization is less than or equal to 1mm^2 . The immobilization conditions and concentration of immobilized reagent would have
20 afforded the same amount of immobilized antibody as that suggested in the instant specification. Chang immobilized 0.05 uL of antibody at a concentration of 10 ug/mL which is a total of 2×10^9 molecules. Applicant immobilized 0.5 uL of antibody at 80 ug/uL which is a total of 1.6×10^{11} molecules and determined that this resulted in 5×10^9 molecules being bound.
25 The adsorption conditions of applicant and Chang are quite similar so that it seems reasonable that a similar proportion of the Chang antibody would have

permanently adsorbed which would give a value of 6.25×10^7 molecules.

Chang discloses a 200 uL sample volume at column 6 line 8. For this sample volume and an affinity of 10^{10} the value of $0.1V/K$ would be 12×10^7

molecules. The value for the affinity constant is not disclosed by Chang,

5 however, a value of 10^{10} is within the normal range for monoclonal antibodies.

Had Chang utilized a second antibody to label the cells it would be anticipatory.

Claims 12 and 23. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the device of Chang with sample volumes such that the amount of immobilized antibody was less

10 than or equal to $0.1 V/K$ because this is less than the maximal amount of antibody which Ekins teaches may be employed to obtain volume independent results.

Claims 13 and 24. The spot size limitation is taught by Chang. Moreover, one would minimize the spot size so that the density of signal would be higher so
15 that the signal to noise ratio would be greater.

Claims 14 and 25. The device of Chang when used in the method of claim 1 meets this limitation.

Claims 15 and 26. The limitation here is to using the device of claim 1 in which either the volume is ten-fold greater or the amount of antibody is ten fold
20 less. In either event the changes lead to a further decrease in the error of the measurement. Such a decrease is an optimization step within the level of skill of the ordinary artisan. It can be accomplished because the means for detection, e.g., a fluorescence microscope, affords sufficient resolution. One of the problems attendant with using less antibody is a potential decrease in signal
25 to noise so that a measurement above background can be made. But with the ability to localize the antibody to a discrete small spot and a device with the

ability to resolve such spots the problem is resolvable.

Claims 16 and 17. Monoclonal antibodies exhibit affinities in this range and are an obvious choice for this method in view of their use by Chang.

5 Claims 18 and 19. The device of Chang when used as discussed above with regard to claims 1 and 19 meets these limitations.

Claim 20. Both Ekins and Chang teach using antibodies as the immobilized binding agent.

Claim 21. Ekins suggests using fluorescently labelled compounds for detecting bound analyte.

10 Claim 22. By labelling the binding agent and quantifying the fractional occupancy as the ratio of analyte signal to binding agent signal one is controlling for variation in the amount of binding agent which is immobilized at a particular site. One of ordinary skill in the art would perform the measurement in this fashion to control for the variation in coating density
15 between spots.

Claims 26-28. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to manufacture kits containing a surface with a plurality of immobilized antibodies such that less than 0.1 V/K was immobilized thereon and detectably labelled reagents capable of binding to
20 bound analyte because such a kit would reduce the time required for analyzing a plurality of analytes and aid in reducing inter assay variability by employing standardized reagents.

Applicant has previously argued that the examiner has failed to demonstrate where the art teaches the limitation that less than 0.1 V/K antibody
25 be employed. As discussed above Ekins teaches that less than V/K is sufficient. One of ordinary skill in the art is capable of analyzing the binding

equation and would realize that even smaller amounts of antibody would be effective provided the signal to noise ratio permitted detection above background.

5 Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Woodward whose telephone number is (703) 308-3890.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

10 Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is (703) 308-4227.

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MP Woodward
August 11, 1993